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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,904	02/09/2000	John B Harley	OMRF 161 CIP	3202

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	46

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,904	HARLEY ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-10 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant requests clarification regarding whether changes to the specification were entered for the submissions of October 24, 2001 or July 31, 2001.

The first substitute specification was submitted on August 10, 2001. This specification was not entered because it did not have the required marked-up version of the replacement paragraph and it did not contain a clean version of the replacement paragraph. This is stated in a communication to applicant in paper no. 19 mailed August 24, 2001. The next submission of a substitute specification was submitted August 14, 2002 (paper no. 36). This substitute specification has been entered.

Applicant also notes that there is no signed copy of a PTO-1449 of the supplemental disclosure statement mailed November 7, 2001.

In response, a full review of the file history does not show a supplemental PTO-1449 submitted November 7, 2001. There have been two PTO-1449 submitted by applicant in the instant case. The first was submitted July 5, 2001 (paper no. 15). The only supplemental PTO-1449 was submitted January 30, 2002 (paper no. 28). Both PTO-1449's were considered, signed and sent to applicant with the final rejection mailed May 8, 2002 (paper no. 29).

Applicant also states that the examiner refers to a paper no. 37, but that no paper 37 can be identified in the file.

Unfortunately, applicant did not state where this reference is being made, so the examiner is unable to assist applicant with the exact reference. However, the file indicates that paper no. 37 is a request for an extension of time.

In paper no. 44, applicant indicates that claims 1-5, 11-18 and 23-26 have been cancelled and that claims 6-8 and 19-21 have been amended. Claims 6-10 and 19-22 are pending and under consideration.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6-10 and 19-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 35 of copending Application No. 08/781,296 for reasons of record. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant did not respond to this rejection, which is maintained for reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-10 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting the presence of EBV, does not reasonably

provide enablement for predicting the risk of developing lupus by detecting the presence of EBV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record.

Applicant describes the invention in detail and asserts that the examiner's comment on page 10 is unjustified because the examples clearly establish a statistically significant relationship between lupus and EBV. Applicant argues that there is no other legal requirement. Specifically, applicant argues that the examples shown in the disclosure are not hypothetical and demonstrate that the instant peptides can be used to distinguish between patients that will develop disease and those that will not. Applicant also cites court decisions, which state that the fact that experimentation will be complex does not necessarily make it undue and that the specification need not provide an example if the skilled artisan can practice it without an undue experimentation. Applicant asserts that the examiner has not provided any evidence that the claims require an undue experimentation.

Contrary to applicant's assertions, the Office has addressed each of the *Wands* factors and has clearly explained why the disclosure and the working examples do not satisfy the enablement requirement. These factors are as follows:

(A) The breadth of the claims: drawn to a diagnostic test comprising reagents used to detect the presence of EBV.

(B) The nature of the invention; drawn to a diagnostic test and a method for predicting the likelihood an individual infected with EBV will develop lupus by comparing control samples

from patients not at risk for developing lupus with patient samples. However, there is no known predictive indicator to distinguish individuals that will develop lupus from those that will not.

(C) The state of the prior art; the prior art does not recognize a nexus between the presence of EBV and developing lupus. The abstracts applicant offer no conclusive data that would indicate that exposure to EBV leads to a greater risk of developing lupus than any other disease. The skilled artisan would be unable to select the appropriate "controls" required by the instant test kit and method because James et al. teach a majority that have been exposed to EBV and do not have lupus. James et al. does not provide data that would indicate factors that a subject would be more likely for developing lupus or any other disease upon EBV exposure. There is no data in the prior art or the specification that would indicate that exposure to EBV is a risk factor for developing lupus or that detecting an antibody to EBV would indicate a predisposition for developing lupus. Marchini et al. (Journal of Autoimmunity. 1994; 7: 179-191) teaches detection of lupus requires the detection of anti-EBNA antibodies as well as autoantibodies specific for SmD, see the abstract and the discussion section. The teachings of Marchini et al. clearly demonstrate that the instant claims are deficient for detecting the risk of developing lupus since more than one factor is required to assay for lupus. With respect to predicting the onset of autoimmune disease, Carson teaches that there are many obstacles for predicting autoimmune disease. Family and population studies indicate that several genes can increase susceptibility of autoimmune disease or influence immune responses to infectious agents that may trigger autoimmunity.

(D) The level of one of ordinary skill; Although it is well within the skill of those in the art to detect the presence of EBV, predicting whether a patient will develop lupus by detecting the presence of EBV is beyond the skill of the ordinary artisan.

(E) The level of predictability in the art; The predictability for determining whether an individual will develop an autoimmune disease, i.e. lupus, is very low.

(F) The amount of direction provided by the inventor; Although data in the specification demonstrates cross-reactivity with specific peptides between EBV and lupus, the assumption that EBV causes or that it is indicative of a possible development of lupus is unsubstantiated.

(G) The existence of working examples; Although the application clearly demonstrates cross-reactivity with specific peptides between EBV and lupus, the assumption that EBV causes lupus or any other autoimmune disease is inconclusive.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is determined that an undue quantity of experimentation would be required for one skilled in the art to use the invention in its full scope due to the lack of data in the prior art, the disclosure and the working examples indicating a nexus between EBV and the development of lupus, the lack of direction provided that the inventor enabling the skilled artisan a way to select appropriate "controls" that will not develop lupus, the lack of predictability for whether an individual will develop lupus, and the level of skill for being able to predict the onset of disease. Applicant has not obviated any of the issues discussed above to satisfy the enablement requirement.

Applicant also discusses court conclusions regarding utility and written description. However, these arguments are irrelevant since the rejection is a scope of enablement and not a utility or a written description rejection.

Applicant also argues that the skilled artisan would have no trouble interpreting the claims for determining what is intended by "means" in the claims. However, this rejection was a § 112, second paragraph rejection and was not under § 112, first, so it is not clear why applicant is arguing this issue in this section. The Office clearly indicates at the bottom of page 7 that it is well within the skill of those in the art to detect the presence of EBV, but predicting whether a patient will develop lupus by detecting the presence of EBV is beyond the skill of the ordinary artisan. Applicant's explanation of "means" does not remedy the lack of skill for the skilled artisan to be able to predict disease manifestation by detecting the presence of EBV.

Applicant also offers a rebuttal for a rejection concerning "likelihood" and "at risk". However, there is no rejection of record concerning these terms in the previous Office action, so it is not clear why applicant is arguing nonexistent issues. Applicant argues that there does not have to be a cause and effect relationship between EBV and lupus to satisfy the legal standard.

However, there must be some evidence provided in the prior art or the specification that there is a correlation between EBV and lupus. The claims are deficient for detecting the risk of developing lupus since the prior art indicates that more than one factor may be a contributor for developing lupus, see the teachings of Carson. Dror et al. (provided by applicant) states in the first sentence that lupus "...is a multisystem disease of unknown origin..." Further, James et al. (also provided by applicant) demonstrates that while almost all 196 lupus patients screened had prior exposure to EBV compared with other viruses, the 95% of the "controls had also been

previously exposed to EBV. It is determined that there is no data in the prior art or the specification that would indicate that exposure to EBV is a risk factor for developing lupus or that detecting an antibody to EBV would indicate a predisposition for developing lupus. Applicant has offered no evidence to remedy these concerns.

Applicant also asserts that the examiner failed to examine the dependent claims because no rational is provided for why the peptides shown to have reactivity in patient sera before and after disease, are not in compliance with § 112, first paragraph.

In response, dependent claims 8, 9, 21 and 22 recite SEQ ID NO: 7. Pages 8-9 of the previous Office action provide a section entitled, "The existence of working examples". In this section, the rejection points directly at the insufficient data for predicting the development of autoimmune disease regarding SEQ ID NO: 7 in the working examples. With respect to the other dependent claims, these claims are also incorporated into the rejection because predicting the risk of developing lupus is not enabled. Reasons for this are discussed throughout the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-10 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. or Marchini et al. and Petersen et al. in the alternative.

The claims are drawn to a diagnostic test and a method to detect levels of antibodies to Epstein-Barr Virus, wherein reagents used to detect antibodies are peptides consisting of specific sequences.

Marchini et al. teach detecting levels of antibodies to EBV compared to control sera, see the abstract and Table 1 on page 183.

Petersen et al. also teach detecting levels of antibodies to EBV compared to control sera, see the Materials and Methods section on page 995 and Figure 5.

Petersen et al. teach the amino acid sequence corresponding to the EBV nuclear antigen-1 (EBNA-1). Petersen et al. also teach specific peptides derived from EBNA-1 that detect levels of EBV antibodies, see Figure 1 and Table 1 on page 994. Although neither Petersen et al. nor Marchini et al. teach the peptides consisting of the sequences claimed, Petersen et al. teach forming small peptides from the EBNA-1 protein that are cross-reactive with EBV antibodies. The peptides claimed in the instant application are also portions of the EBNA-1 protein and correspond to the peptide sequences taught by Petersen et al. For example, SEQ ID NO: 100 is contained in the E3 peptide taught by Petersen et al. and SEQ ID 38 has matches the C terminal half of E14 and the N terminal half of E11, while SEQ ID NO: 107 overlaps 38 in the E11 portion and ends with the C terminal half of E11. A glycine-alanine rich peptide, P62, was reactive in RA patients and convalescent mononucleosis patients, but had no cross-reactivity with host proteins, see the second paragraph on page 994 and figure 5 on page 997. From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation in producing the claimed invention because of the clear difference in epitope specificity in each group of patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to derive peptides from EBNA-1, taught by Petersen et al., to detect EBV antibodies in the method taught by Petersen et al. or Marchini et al. and Petersen et al. to determine which portion of the EBNA protein a patient has specific antibodies to. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the peptide derivatives disclosed by Petersen et al. to further identify epitopes distinguishing between different subject populations. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for detecting EBV antibodies to peptides derived from EBNA-1 because Petersen et al. teach that peptides derived from EBNA-1 are cross-reactive with EBV-antibodies. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Applicant argues that neither Marchini et al. nor Petersen et al. teach that one can predict the likelihood of developing lupus based on an EBV infection. However, the intended use is not a claim limitation. It does not require steps to be performed and does not limit the scope of the claims, see MPEP § 2111.02.

Applicant also argues that Petersen et al. teach away from the claimed invention because the reference only evaluates patients after they have developed autoimmune disease and the claims require testing prior to the development of the disease.

The claims have been fully reviewed. However, the limitation discussed by applicant is not recited.

Applicant also argues that the reagents are not rendered obvious over Petersen et al. because a reasonable expectation of success has not been presented.

The teachings of Petersen have been fully reviewed and applicant's arguments have been fully considered, but are found unpersuasive. Petersen et al. clearly teach that peptides derived from EBNA-1 are cross-reactive with EBV-antibodies. Therefore, one of ordinary skill in the art at the time the invention was made would have had a more than reasonable expectation of success for detecting EBV antibodies to peptides derived from EBNA-1. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley

JAMES HOUSEL 11/3/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600